REMARKS

1. Preliminary Matter

a. Status of the Claims

Claims 31-36 and 39-42 are pending in this application. Claims 31, 32, and 39-42 are amended; claims 33-36 are canceled without prejudice to pursuing the canceled subject matter in a continuing application. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of these amendments, claims 31, 32, and 39-42 are pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as described in Table A.

Table A

Claim	Support
31	Table 2, lines 6980-7076
32	Table 1, line 724; Table 2, lines 6980-7076
39	as described for amended claim 31, paragraphs 0043-0045
40	as described for amended claim 32, paragraphs 0043-0045
41	as described for amended claim 31, paragraph 0043
42	as described for amended claim 32, paragraphs 0043

c. Interview Summary

The undersigned thanks Examiners Wollenberger, Angell, and Schultz for the courtesy of the personal interview conducted on November 8, 2007, at which the utility rejection was discussed.

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 3-6 of the Office Action, the Examiner maintains the rejection of claims 31-36, and 39-42 under 35 U.S.C. § 101, for allegedly lacking utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher* 421 F.3d 1365, 1371 (2006) and *Revised Interim Utility Guideline Training Materials* ("Guidelines").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See In re Fisher* 421 F.3d at 1371 and Guidelines. Applicant respectfully submits that the application provides a specific

utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The Fisher application did not disclose the location of the ESTs in the genome or the function of the underlying genes. Fisher asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Id.* at 1367 and 1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids maybe used to target and modulate expression of **specific** gene transcripts. As the Examiner acknowledges at page 3 of the Office Action, the claimed nucleic acids are capable of specifically regulating the expression of Choline Acetyltransferase (ChAT). Likewise, Table 8, lines 7222-7243 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the SERPINA3 gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene SERPINA3**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the SERPINA3 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See In re Fisher* at 1371 and the Guidelines. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *In re Fisher* and the Guidelines.

In Fisher, it was admitted that the underlying genes for the ESTs had no known function. Fisher argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, Fisher failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Id.* at 1373 quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of SERPINA3. *See* Table 7, lines 1488-1492. At the time of filing, it was known in the art that SERPINA3[1] is a chymotrypsin type serine proteinase inhibitor. *See* Ikari *et al.* (*JBC* 2001;276(15):11798–11803). SERPINA3 functions as a plasma proteinase inhibitor which protects against the degradation of extracellular matrix proteins by cell-derived proteinases, and is essential to ensure appropriate cell-matrix interaction. At the time of filing, SERPINA3 was also known to be capable of functioning as an antiapoptotic factor for human vascular smooth muscle cells *in vitro*. High levels of SERPINA3 protein expression in serum indicated that it is one of the major antiapoptotic serum proteins. It was further known that serum concentrations of SERPINA3 increase rapidly and dramatically after a variety of events including surgery, burn injury, inflammatory bowel disease, and some types of cancer.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. One such benefit is the ability to modulate expression of SERPINA3 in order to modulate the level of apoptosis in human smooth muscle cells, such as in the vasculature. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requires are satisfied in accordance of Fisher and the Guidelines.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would

[1] SERPINA3 is also referred to as "alpha-1 antichymotrypsin," "α1ACT," and "serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3."

conclude that the asserted utility is more likely than not true. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of the SERPINA3 mRNA transcript. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. See paragraphs 2 and 3 of the Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. See paragraph 3 of the Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. See paragraph 3 of the Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. See paragraph 3 of the Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 15 and its target gene sequence of SERPINA3 (as depicted in Column B, Row 3, Page 3 of Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. See paragraph 6. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 15 (Column B, Row 3, Page 3 of Table A) is likely to inhibit expression of the protein encoded by the target gene SERPINA3 in view of the characteristics of microRNA:mRNA binding properties. See paragraph 6 of the Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. See paragraph 4 of the Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al., Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorigthm; where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. See Paragraph 4 of the Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 15 and its target gene sequence of SERPINA3 are consistent with microRNA and target mRNAs predicted by the algorithms described above. See paragraphs 4 and 5 of the Pilpel Declaration. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 15 is likely to inhibit expression of the protein where co-expressed. See paragraph 6 of the Pilpel Declaration.

(c) SERPINA3

Applicant further submits that SERPINA3 is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the nucleic acid having the sequence as set forth in SEQ ID NO: 15 has been biologically validated. See Row 3, Page 3 of Table A. Accordingly, SERPINA3 is an important target in nature by trans-acting elements such as microRNAs. Furthermore, the Examiner acknowledges on page 5 of the Office Action that it is credible that the claimed nucleic acids may be used to inhibit the expression of a ChAT gene. The claimed nucleic acids are capable of binding to the ChAT mRNA with a19 out of 22 base complementation. Likewise, the claimed nucleic acids are capable of binding SERPINA3 with a 18 out of 22 nucleotides of complementation, as demonstrated at Table 7, lines 1468-1501 of the specification, and as shown below.

GAM NAME	GAM RNA SEQUENCE	TARGET	TARGET REF-ID	UTR	TARGET BS-SEQ	BINDING-SITE DRAW (UPPER:GAM;LOWER:TARGET)	GAM POS
GAM1032	CTAGACTGAAG	SERPINA	NM_001085.2	3	GCCCATGGACTCT	C- T A A	A
	CTCCTTGAGGA	3			TCAGTCTGG	CTAGACTGAAG TCC TG GG	
						GGTCTGACTTC AGG AC CC	

In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of SERPINA3, which in turn would modulate the level of apoptosis in human smooth muscle cells. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

b. 35 U.S.C. § 112, first paragraph

On page 6 of the Office Action, the Examiner asserts that because the claimed subject matter lacks substantial utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

c. 35 U.S.C. § 102(b)

In view of NEB Random Primer 24

On pages 6-8 of the Office Action, the Examiner rejects claims 31-36, 41 and 42 under 35 U.S.C. § 102(b) as allegedly being anticipated by Random Primer 24, sold by New England Biolabs in the 1998/99 catalog ("NEB"). The Examiner asserts that NEB teaches a vial containing 9 copies of every possible 24-nucleotide sequence, thus meeting the limitation of claim 31(b), "DNA equivalent." The Examiner alleges that the specification on page 8 contains no clear or limiting definition of the term "isolated" of claim 31 that would clearly preclude isolated mixtures of oligonucleotides of the type sold and disclosed by NEB. Applicant respectfully disagrees and submits that the Examiner's rejection is solely an issue of whether an "isolated" nucleic acid is taught by NEB .

The term "isolated" has a clear meaning to one of skill in the art. As the Examiner notes on page 7, NEB teaches a vial containing over 2.81×10^{14} possible 24-nucleotide sequences. Even if one such tube contained a nucleic acid with the sequence of the claimed nucleic acid, NEB teaches this nucleic acid as only one among 2.81×10^{14} nucleic acids in the vial. One sequence among 2.81×10^{14} is not an isolated nucleic acid. Accordingly, NEB does not specifically teach the sequences of the instantly claimed nucleic acids.

With regard to the term "DNA Equivalent," Applicant submits that if one of skill knows the RNA sequence, they will also know the DNA sequence. Nevertheless, to expedite prosecution and without prejudice to seeking DNA equivalents in a continuing application, "DNA equivalent" has been removed from amended claims 31 and 32.

Finally, amended claim 31 is further related to a sequence of 131 nucleotides in length, and amended claim 32 is related to a sequence of 22 nucleotides. Accordingly, NEB teaches only 24-mers and does not disclose the isolated claimed nucleic acids, and therefore does not teach all the limitations of either amended claim 31 or 32. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 31-36, 41, and 42 under 35 U.S.C. § 102(b) in view of NEB.

In view of US 6,582,908

On pages 8 and 9 of the Office Action, the Examiner rejects claims 31-36, 41, and 42 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fodor *et al.* (U.S. Pat. No. 6,582,908; "Fodor"). The Examiner asserts that Fodor teaches a nucleic acid array comprising all possible 20-mers, thereby anticipating DNA equivalents of the instantly claimed nucleic acids. Applicant respectfully disagree.

As discussed above, amended claims 31 and 32 do not recite a "DNA equivalent." Instant claims 31 and 32 are directed to isolated nucleic acids. The array of Fodor cited by the Examiner comprises nearly 1.1×10^{12} different sequences. One sequence among 1.1×10^{12} is not isolated. Accordingly, Fodor

does not teach all the limitations of either amended claim 31 or 32. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 31-36, 41, and 42 under 35 U.S.C. § 102(b) in view of Fodor.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: February 4, 2008

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